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Assoc Prof
KAWABATA, Takeo
(D Pharm Sc)

Instr
TSUBAKI, Kazunori
(D Pharm Sc)

Techn
TERADA, Tomoko

Guest Res Assoc
BAGUL, D. Trusar
(Ph D)

Guest Res Assoc
ÖZTÜRK, Orhan
(Ph D)

Guest Res Assoc
SCHEDEL, Hartmut
(Ph D)

Guest Res Assoc
MAJUMDAR, Swapan
(Ph D)

Students

OHTSUBO, Tadamune (D3)
KUSUMOTO, Tomokazu (D1)
NAGAOKA, Yoshie (M2)
OKAZAKI, Akira (M1)
TANAKA, Hiroyuki (D2)
HIRASE, Keizo (M2)
ISOBE, Fumiko (M1)
SHIMADA, Shoko (M1)
KAWAKAMI, Shin-pei (D1)
MORIKAWA, Hiroshi (M2)
MARUOKA, Hiromi (M1)
TANIMA, Daisuke (M1)
SHIRAI, Ryo (RS)

Scope of Research

The research interests of the laboratory include the development of new synthetic methodology, total synthesis of biologically active products, and molecular recognition. Programs are active in the areas of asymmetric alkylation of carbonyl compounds based on "memory of chirality", nucleophilic catalysis for selective reactions, synthesis of unusual amino acids, visualization of molecular chirality by functionalized phenolphthalein, use of homooxacalixarene for molecular recognition, and the structural and functional investigation of homo- and heterochiral oligomers.

Research Activities (Year 2002)

Presentations

Asymmetric Synthesis based on Dynamic Chirality of Enolates, Kawabata T, Annual Meeting, Chem. Soc. Jpn., 26 March.

Aymmetric Alkylation of Amino Acid Derivatives under the Control of Aggregation of Enolates, Kawabata T, Kawakami S, *et al.*, Annual Meeting of the Pharmaceutical Society of Japan, 27 March.

Visual Enantiomeric Recognition of Alanine Derivatives, Tsubaki K, Nuruzzaman M, *et al.*, Symposium on Molecular Chirality, 6 June.

Synthesis and Functions of New Homooxa-calix[3]arene Derivatives, Tsubaki K, Maruoka H, Otsubo T, *et al.*, 52th Meeting of the Pharmaceutical Society of Japan (Kinki). 19 October.

Achiral Auxiliaries for Asymmetric Induction, Kawabata T, Öztürk O, *et al.*, 28th Symposium on Progress in Organic Reactions and Syntheses, 5 November.

Synthesis and Functions of Chiral Origo Naphthalene Derivatives, Tsubaki K, Morikawa H, *et al.,* 17th Meeting of Cyclophane Chemistry. 8 November.

Nuceophilic Catalysis in Kinetic Resolution of Racemic Alcohols, Kawabata T, International Symposium on Biotechnology, Metal Complexes and Catalysis, 26 Novemmber.

Grants

Kawabata T, Aymmetric Synthesis through Nucleophilic Catalysis, Grant-in-Aid for Scientific Research (B) (2), 1 April 1999 - 31 March 2002.

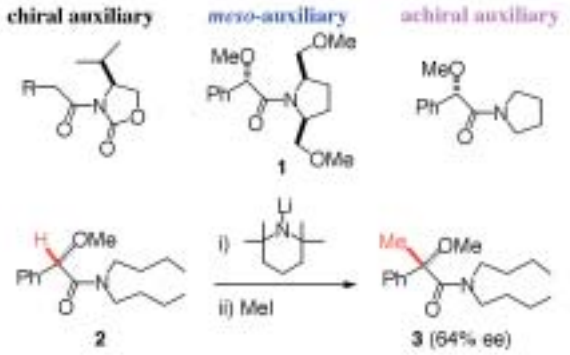
Kawabata T, Development of a New Generation of Nucleophilic Catalysts and Selective Reactions, Grant-in-Aid for Scientific Research (B) (2), 1 April 2002 - 31 March 2005.

Tsubaki K, Visualization of Molecular Information using Phenolphthalein Derivatives. Grant-in Aid for Scientific research (C) (2), 1 April 2002 - 31 March 2004.

The former professor Kaoru Fuji retired on 31 March 2002.

Achiral Auxiliaries for Asymmetric Induction

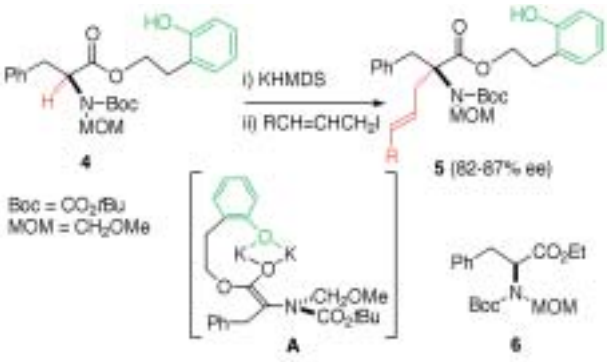
Chiral auxiliary is frequently used in asymmetric synthesis. It is still the most reliable and predictable method for the preparation of optically active natural products. It was long believed that auxiliaries have to be chiral to cause any asymmetric induction. However, we found that *meso*-2,5-disubstituted pyrrolidine can be used as an auxiliary for asymmetric induction. For example, methylation of **1** proceeded in 73% ee by treatment with *n*-BuLi/TMEDA in cyclopentyl methyl ether (CPME) followed by addition of methyl iodide. We further found that even achiral amines such as pyrrolidine and dibutyl amine can be used as auxiliaries for asymmetric induction. Treatment of **2** with lithium 2,2,6,6-tetramethylpiperidide in CPME followed by addition of methyl iodide gave **3** in 64% ee in retention of configuration. A mixed aggregate consisting of an achiral enolate and an undeprotonated chiral amide is proposed as a crucial intermediate for the asymmetric induction.



Enantioselective allylation of amino acid derivatives under the control of aggregate structure of chiral nonracemic enolates

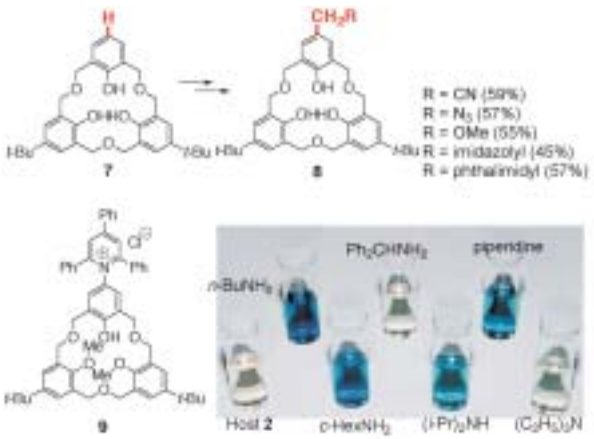
Control of aggregation of enolates is one of the long-standing problems in enolate chemistry. Addition of strongly coordinating ligands such as HMPA or TMEDA is a typical approach to this issue. A new approach by formation of intramolecular mixed aggregate with pseudo-enolate subunit is shown here. Enolates usually exist as a mixture of different aggregates in solution, such as the case of an enolate generated from ethyl ester **6**. The complexity of the aggregates often causes difficulties in controlling selectivity of the reactions. Phenylalanine derivative **4** with a phenol group (pseudo-enolate subunit) was designed to form stable intramolecular aggregate **A** as a single aggregate species on treatment with a base.

α-Allylation of **4** proceeded in 82~87% ee, which is greatly improved than that of **6** (23~69% ee). It was also found that formation of an intramolecular aggregate enhances kinetic stability of a chiral nonracemic enolate against racemization; a half-life to racemization of a potassium enolate generated from **4** is *ca.* ten times as long as that generated from **6**. In both cases, chirality of the starting materials is preserved in the enolate intermediates as C-N axial chirality of a dynamic nature. Optically active α-allylated amino acids are versatile intermediates for functional peptides.



Chromogenic Homooxacalix[3]arene Receptor

Homooxacalix[3]arene is related to calix[4]arene and 18-crown-6 ether with unique structural features. It has been known, however, that difficulties arose in the transformation of functional groups on the upper rim due to the presence of three fragile dibenzyletheral linkages. We describe here, for the first time, the introduction of functional groups on the upper rim through successive reactions of **7** (i.e. the Mannich reaction, exhaustive methylation, *p*-quinone methide formation, and nucleophilic substitution) in 45-59% overall yields. The artificial host molecule **9**, consisting of homooxacalix[3]arene and pyridinium *N*-phenolate dye (Reichardt dye E_T1) has been prepared. Host **9**, with a proton-ionizable phenol group that acts as chemical switch, causes color change against alkaline metals and various kind of amines.



Award

Tsubaki K, The ICR Award for Young Scientists, Molecular Recognition using Phenolphthalein Derivatives, ICR, 6 Decmber.

Morikawa H, Best Poster Award, Effective Synthesis of Chiral Origo-Naphthalene Derivative, The Pharmaceutical Society of Japan (Kinki) and the Society of Synthetic Organic Chemistry, Japan (Kansai), 10 December.